(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 June 2004 (03.06.2004)

PCT

(10) International Publication Number
WO 2004/046323 A2

(51) International Patent Classification[7]: C12N

(21) International Application Number:
PCT/US2003/036548

(22) International Filing Date:
14 November 2003 (14.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/426,665	15 November 2002 (15.11.2002)	US
60/426,668	15 November 2002 (15.11.2002)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US	60/426,665 (CIP)
Filed on	15 November 2002 (15.11.2002)
US	60/426,668 (CIP)
Filed on	15 November 2002 (15.11.2002)

(71) Applicant *(for all designated States except US)*: **THE SALK INSTITUTE FOR BIOLOGICAL STUDIES** [US/US]; 10010 North Torrey Pines Road, La Jolla, CA 92037 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DOWNES, Michael, R.** [AU/US]; 3440 Lebon Drive, Apt. 4210, San Diego, CA 92122 (US). **VERDICIA, Mark, A.** [US/US]; 79-11 Sutter Avenue, New York, NY 11417 (US). **NOEL, Joseph, P.** [US/US]; 14428 Rock Rose, San Diego, CA 92127 (US). **EVANS, Ronald, M.** [US/US]; 1471 Cottontail Lane, La Jolla, CA 92037 (US). **BOWMAN, Lindsey, J.** [US/US]; 10034 Riverhead Drive, San Diego, CA 92129-3217 (US). **BOWMAN, Marianne** [US/US]; 10034 Riverhead Drive, San Diego, CA 92129-3217 (US).

(74) Agents: **REITER, Stephen, E.** et al.; Foley & Lardner, P.O. Box 80278, San Diego, CA 92138-0278 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STRUCTURE OF THE FARNESOID X RECEPTOR LIGAND BINDING DOMAIN AND METHODS OF USE THEREFOR

(57) Abstract: The present invention provides compositions comprising the ligand binding domain (LBD) of a farnesoid X receptor (FXR) in crystalline form. In alternative embodiments, the LBD of FXR is complexed with a ligand therefor. There are provided high resolution structures of FXR complexed with a novel high affinity agonist, fexaramine. The discovered structure of a FXR LBD provides the first three-dimensional view of the structural basis for FXR ligand binding. The present invention further provides a computer for producing a three-dimensional representation of FXR or a complex thereof, and a computer for determining at least a portion of the structure coordinates of FXR or a complex thereof. The present invention further provides methods of using this structural information to predict molecules capable of binding to FXR; to identify compounds with agonist, antagonist or partial agonist activity for FXR; and to determine whether a test compound is capable of binding to the LBD of FXR. The present invention further provides compositions comprising compounds identified by such invention methods.

WO 2004/046323 A2